PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

B1

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 93/21179
C07D 403/06, 401/06, 405/06 C07D 295/073, 295/125, 295/135 C07D 209/48, C07C 309/73 A61K 31/495	A1	(43) International Publication Date: 28 October 1993 (28.10.93)

(21) International Application Number: PCT/SE93/00295

(22) International Filing Date: 6 April 1993 (06.04.93)

(30) Priority data:
9201138-6 9 April 1992 (09.04.92) SE

(71) Applicant: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE).

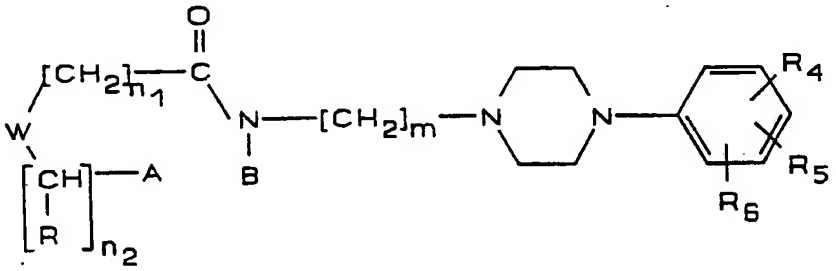
(72) Inventors: BENGTSSON, Stefan ; Pärongränd 4, S-151 68 Södertälje (SE). FLORVALL, Lennart ; Snickarstigen 7, S-151 59 Södertälje (SE). HALLNEMO, Gerd ; Nydalavägen 58, S-151 51 Södertälje (SE). JACKSON, David ; Kämpevägen 31 II, S-151 54 Södertälje (SE). ROSS, Svante ; Hedvägen 8, S-151 52 Södertälje (SE). TOLF, Bo-Ragnar ; Kaptensgatan 3, S-619 00 Trosa (SE). ULFF, Bengt ; Ägostigen 19, S-151 54 Södertälje (SE). ZHANG, Lian ; Karlhovsvägen 17, S-151 52 Södertälje (SE). ÅKESSON, Christina ; Kottestigen 87, S-147 43 Tumba (SE).

(74) Agents: DANIELSSON, Sten et al.; Aktiebolaget Astra, Patent Department, S-151 85 Södertälje (SE).

(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL AMIDOALKYL- AND IMIDOALKYL-PIPERAZINES



(I)

(57) Abstract

Compounds of general formula (I) wherein R is a hydrogen atom or a phenyl group, m is an integer 3 to 8, R_4 is an NO_2 group or a group NR_7R_8 wherein R_7 and R_8 are the same or different and each is hydrogen or alkyl, R_5 is hydrogen, halogen or CF_3, R_6 is halogen, or CF_3, W is an optionally substituted aromatic ring(s), a heterocyclic ring, a carbocyclic ring(s), or an optionally substituted methylene group, A is a hydrogen atom, a hydroxy group, a halogen atom, CF_3, an alkyl group, an alkoxy group, a phenyl group, or a phenoxy group, B is a hydrogen atom, or A and B together constitute a carbonyl group, n_1 is 0 or 1, and n_2 is 0 or 1, processes and intermediates for their preparation, pharmaceutical preparation containing them and the use of the compounds in the treatment of mental disturbances.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

Novel amidoalkyl- and imidoalkyl-piperazines

Field of the invention

The present invention relates to novel, 1-aryl-4(ω-amido-1-alkyl and ω-imido-1-alkyl)piperazines, intermediates and processes for their preparation, pharmaceutical compositions containing the piperazines and to the use of said compounds in therapy.

The object of the present invention is to provide novel compounds that will be useful in the treatment of psychiatric disorders such as schizophrenia and other psychoses, anxiety, depression and manic-depressive psychosis.

Prior art

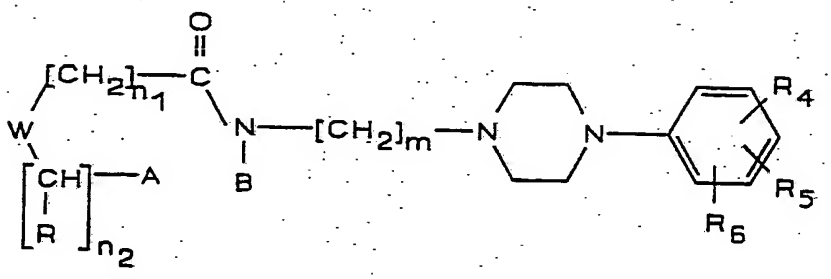
Buspirone is a known substance that has been recently tested in a variety of central nervous system diseases including depression. It has affinity for both 5HT1A receptors and for D2 receptors.

Glennon and colleagues (Glennon RA, Naiman NA, Lyon RA, Titeler M: Journal of Medicinal Chemistry, 1988, 31, 1968-1971) describe some aryl piperazine derivatives, including NAN190 [=1-(2-methoxyphenyl)-4-(4-(2-phthalimido)butyl)piperazine] that bind to 5HT1A receptors as labelled by (3H)-8-hydroxyDPAT. In another report, the same group (Raghuparthi RK, Rydelek-Fitzgerald L, Teitler M, Glennon RA: Journal of Medicical Chemistry 1991, 34, 2633-2638) describe some analogs of the 5HT1A agonist NAN190 that have affinity at 5HT1A receptors, as well as some binding affinity at α1 receptors. Further synthetic work in a related area is also described (Glennon RA, Naiman NA, Pierson ME, Smith

JD, Ismaiel AM, Titeler M, Lyon RA: Journal of Medicinal Chemistry 1989, 32, 1921-1926).

Disclosure of the invention

According to the present invention it has been found that new compounds of the general formula



I

or pharmaceutically acceptable salts thereof, wherein

R is a hydrogen atom or a phenyl group,

m is an integer 3 to 8,

R_4 is situated in the meta or para position of the ring and represents an NO_2-group or a group NR_7R_8 wherein R_7 and R_8 are the same or different and each represents a hydrogen atom or an alkyl group having 1-3 carbon atoms,

R_5 is situated in the ortho, meta or para position and represents a hydrogen atom, a halogen atom, or CF_3,

R_6 is situated in the ortho, meta or para position and represents a halogen atom or CF_3,

W is an optionally substituted aromatic ring(s), a

heterocyclic ring, a carbocyclic ring(s), or an optionally substituted methylene group,

A is a hydrogen atom, a hydroxy group, a halogen atom, CF_3, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group,

B is a hydrogen atom, or

A and B together constitute a carbonyl group,

n_1 is 0 or 1, and

n_2 is 0 or 1,

in racemic or optically active form, or as a mixture of diastereomers, provided that

1) when W is an optionally substituted aromatic ring(s) then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A is a hydrogen atom, a halogen atom, CF_3, a hydroxy group, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group, and
B is a hydrogen atom or
A and B together constitute a carbonyl group,

2) when W is a carbocyclic ring(s) or a heterocyclic ring then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A and B are hydrogen atoms or

A and B together constitute a carbonyl group,

3) when W is an optionally substituted methylene group then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 and n_2 are 1 or
n_1 is 1 and n_2 is 0 or
n_1 is 0 and n_2 is 1,
A and B together constitute a carbonyl group,

exhibit an affinity for D_2 and 5HT1A receptors. This effect makes it possible to use the compounds defined above in the treatment of mental disturbances e.g. psychosis, schizophrenia and depression.

An aromatic ring(s) in the definition above is preferably phenyl or naphthyl and is mono- or disubstituted, wherein the substituents are preferably chosen from the following: a hydrogen atom, a halogen atom, a hydroxy group, CF_3, an alkyl group(s) having 1-3 carbon atoms, or an alkoxy group(s) having 1-3 carbon atoms.

Heterocyclic ring in the definition above is preferably furyl, thienyl, pyrrolyl, pyridyl, or indolyl.

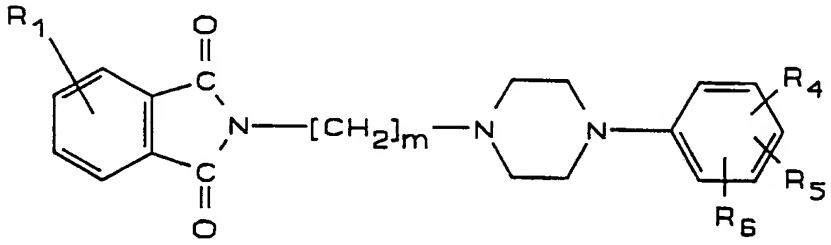
A carbocyclic ring(s) in the definition above is preferably mono, bi, or polycyclic rings having 3-12 carbon atoms.

The substituents on the carbocyclic ring(s) in the definition above are preferably a hydrogen atom or an alkyl group having 1-3 carbon atoms.

The substituent on the methylene group in the definition above is preferably a hydrogen atom or an alkyl group having 1-4 carbon atoms.

Halogen in the definition above is preferably a chlorine, bromine, or fluorine atom.

A preferred group of compounds are those of the general formula



Ia

or pharmaceutically acceptable salts thereof, wherein

R_1 is situated in the 3- or 4-position and represents a hydrogen atom, a halogen atom, CF_3, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, NO_2, $COCH_3$, or NR_2R_3 wherein R_2 and R_3 are the same or different and each represents a hydrogen atom or an alkyl group having 1-6 carbon atoms,

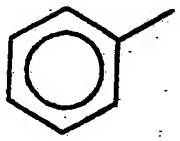
m is an integer 3 to 8,

R_4 is situated in the meta or para position of the ring and represents an NO_2 group or a group NR_7R_8 wherein R_7 and R_8 are the same or different and each represents a hydrogen atom or an alkyl group having 1-3 carbon atoms,

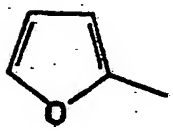
R_5 is situated in the ortho, meta, or para position of the ring and represents a hydrogen atom, a halogen atom, or CF_3,

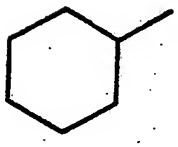
R_6 is situated in the ortho, meta, or para position of the ring and represents a halogen atom or CF_3

W is preferably chosen from the following groups:

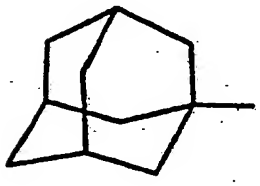
i 

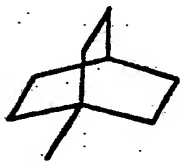
the substituents preferably being a halogen atom, a hydroxy group, or a methoxy group, most preferred are bromine, hydroxy, or methoxy in the ortho and/or meta positions.

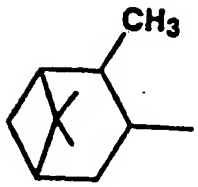
ii 

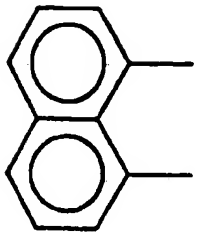
iii 

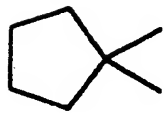
iv 

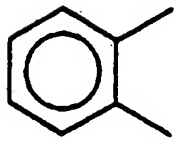
v 

vi 

vii 

viii 

ix 

x 

the substituents being a halogen atom or a methoxy group

xi 

When W is chosen from one of the groups i-xi, then

m is preferably 4-6,

R_4 is preferably NH_2,
most preferred R_4 is NH_2 in the meta or para positions,

R_5 is preferably hydrogen or halogen,
particularly preferred are compounds where R_5 is hydrogen, chlorine, or bromine,
most preferred R_5 are hydrogen or chlorine in the meta or para positions,

R_6 is preferably CF_3 or halogen,
further preferred are compounds where R_6 is CF_3 or chlorine,
most preferred R_6 are CF_3 or chlorine in the meta position.

When W is i-x, then R is preferably H.

When W is i, then
n_1 is preferably 0 and n_2 is preferably 0 or 1,
most preferred n_2 is 0,
A is preferably hydrogen, methoxy, or hydroxy in the ortho position.

When W is ii, then
n_1 is preferably 0.

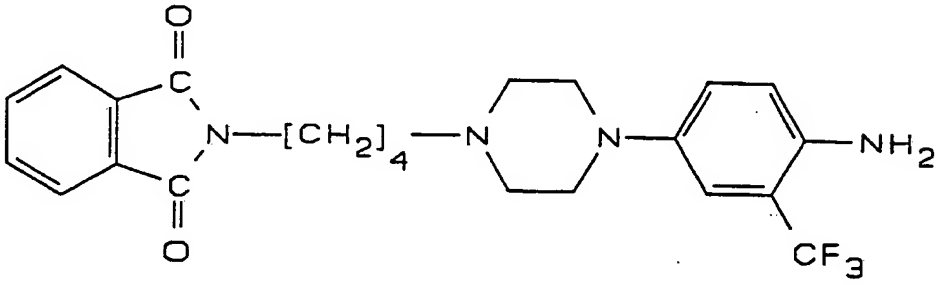
When W is iii-vii, then
n_1 is preferably 0,
A is preferably a hydrogen atom or an alkyl group with 1-3 carbon atoms,
and B is preferably a hydrogen atom.

When W is viii, then
n_1 and n_2 are preferably 0 and
A and B preferably constitute a carbonyl group.

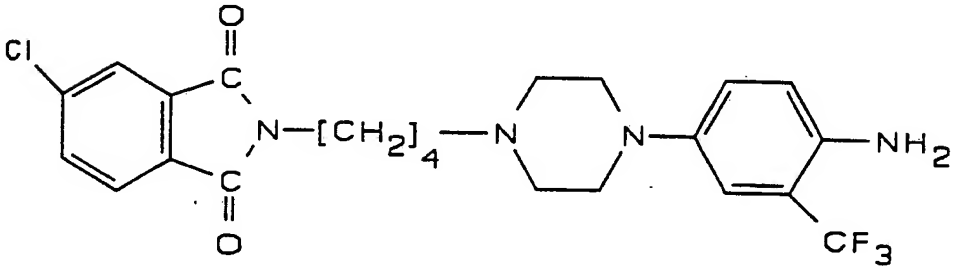
When W is ix, then
n_1 and n_2 are preferably 1 and
A and B preferably constitute a carbonyl group.

When W is x, then
n_1 and n_2 are preferably 0 and
A and B preferably constitute a carbonyl group.

Most preferred are the following compounds

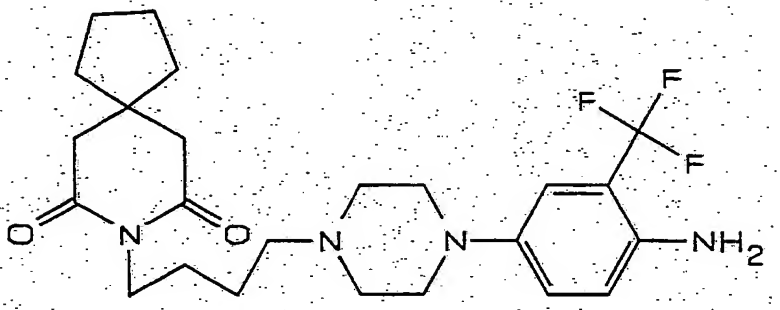


and

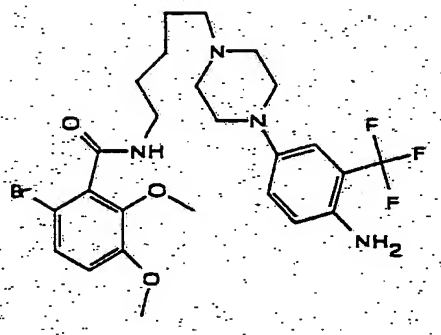


and

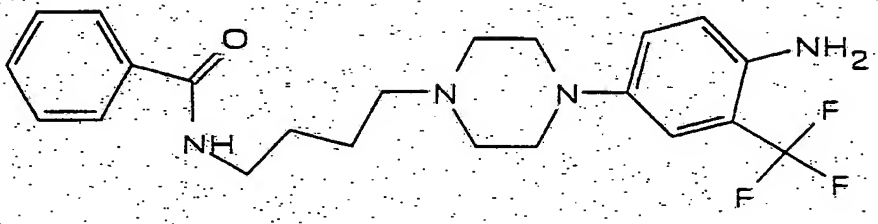
and

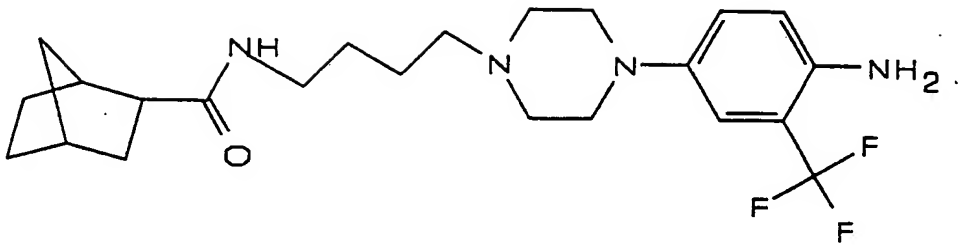


and

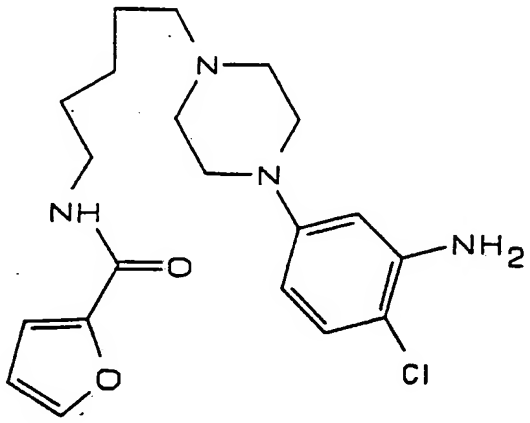


and

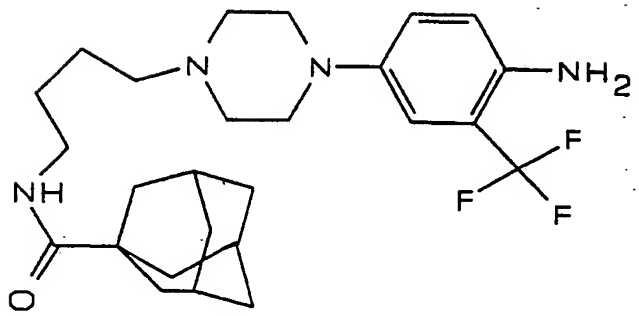




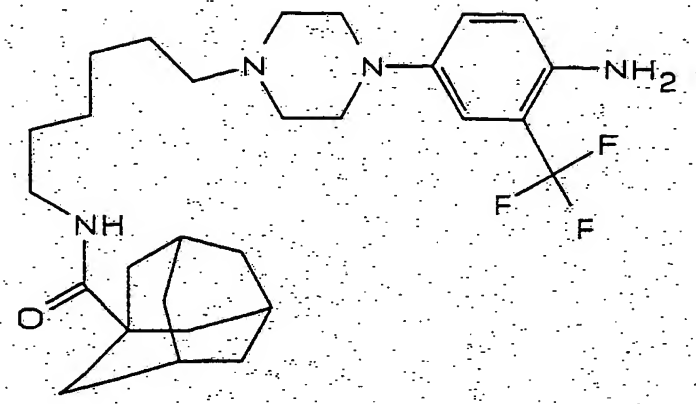
and



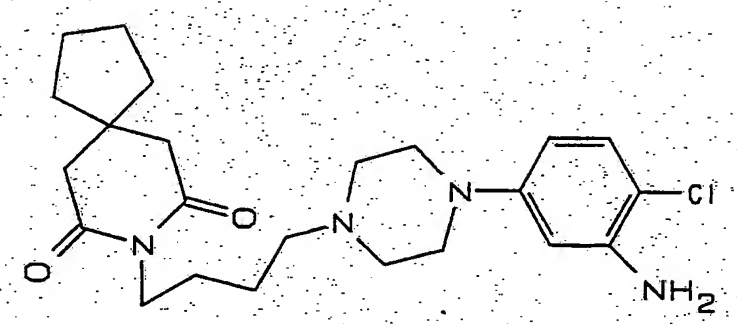
and



and



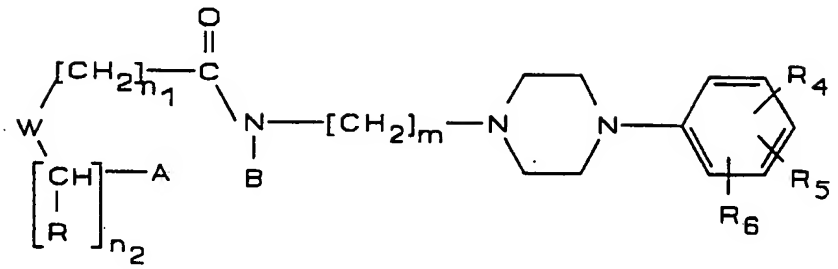
and



Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfamic, succinic, propionic, glycollic, malic, mandelic acid, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic, salicylic, 4-aminosalicylic, 4-hydroxybenzoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These are readily prepared by methods known in the art.

Preparation

The compounds of the general formula I



I

wherein R is a hydrogen atom or a phenyl group,

m is an integer 3 to 8,

R_4 is situated in the meta or para position of the ring and represents an NO_2-group or a group NR_7R_8 wherein R_7 and R_8 are the same or different and each represents a hydrogen atom or an alkyl group having 1-3 carbon atoms,

R_5 is situated in the ortho, meta or para position and represents a hydrogen atom, a halogen atom, or CF_3,

R_6 is situated in the ortho, meta or para position and represents a halogen atom, or CF_3,

W is an optionally substituted aromatic ring(s), a heterocyclic ring, a carbocyclic ring(s), or an optionally substituted methylene group,

A is a hydrogen atom, a hydroxy group, a halogen atom, CF_3, an alkyl group having 1-3 carbon atoms, an alkoxy

group having 1-3 carbon atoms, a phenyl group, or a phenoxy group,

B is a hydrogen atom, or

A and B together constitute a carbonyl group,

n_1 is 0 or 1, and

n_2 is 0 or 1,

in racemic or optically active form, or as a mixture of diastereomers, provided that

1) when W is an optionally substituted aromatic ring(s) then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A is a hydrogen atom, a halogen atom, CF_3, a hydroxy group, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group and
B is a hydrogen atom or
A and B together constitute a carbonyl group,

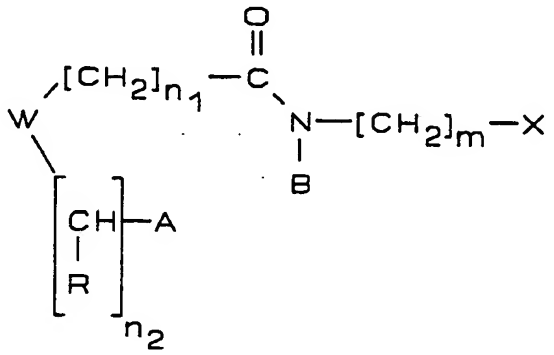
2) when W is a carbocyclic ring(s) or a heterocyclic ring then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A and B are hydrogen atoms or
A and B together constitute a carbonyl group,

3) when W is an optionally substituted methylene group then
R, m, R_4, R_5, and R_6 are as defined above,

n_1 and n_2 are 1 or
n_1 is 1 and n_2 is 0 or
n_1 is 0 and n_2 is 1,
A and B together constitute a carbonyl group,

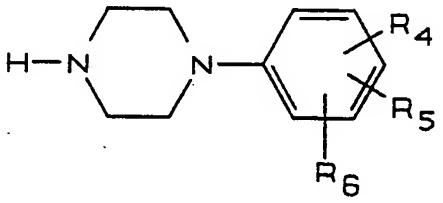
are prepared by any of the following alternative methods.

A) Reaction of a compound of the general formula II



II

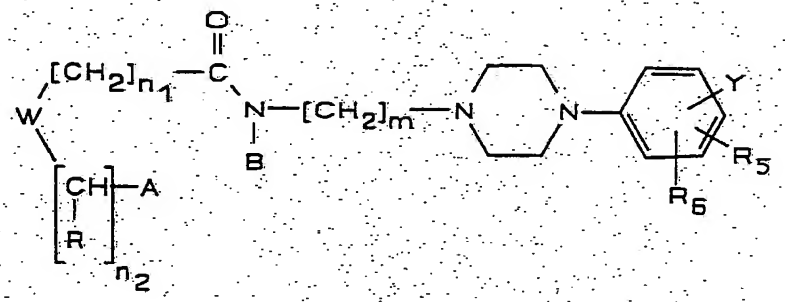
wherein R, m, W, A, B, n_1 and n_2 are as defined above and X is a suitable leaving group such as halogen, arylsulfonate or alkylsulfonate, with a compound of the general formula III



III

wherein R_4, R_5 and R_6 are as defined above in a suitable solvent, such as an alcohol, DMF, acetonitrile or DMSO in the presence of a base such as triethylamine, sodium hydroxide, or potassium carbonate and a catalytic amount of a sodium or potassium halide, such as KI at ambient or higher temperature for a prolonged time.

B) Conversion of a compound of the general formula IV

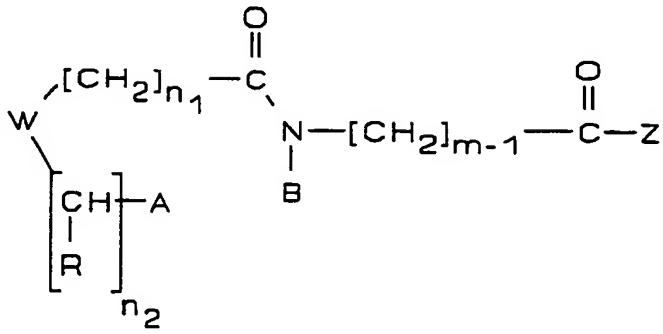


IV

wherein R, m, R_5, R_6, W, A, B, n_1 and n_2 are as defined above and Y is situated in the meta or para position and represents a group which can be transformed to a group $R_4{}^1$, where $R_4{}^1$ is situated in the meta or para position of the ring and represents a group NR_7R_8, wherein R_7 and R_8 are as defined above, by a suitable hydrolytic, reductive, electrochemical or other known processes. Compounds of the formula IV can be prepared according to Method A. Such a group Y may be chosen from easily cleaved amides, carbamates, imines, benzylic amines or other suitably protected amino groups. Such groups can be trifluoroacetamido, formamido, t-butoxycarbonylamino, or N-benzylamino.

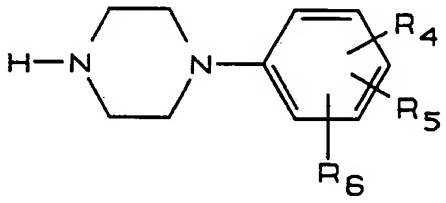
In addition, Y can be a group such as nitro, azido, hydroxyamino, hydrazono, amido or imino, which can be transformed to $R_4{}^1$ by known reductive processes.

C) Reaction of a compound of the general formula V



V

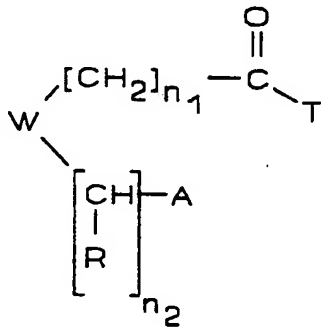
wherein R, m, W, A, B, n_1 and n_2 are as defined above and Z is hydrogen, hydroxy, halogen, or alkoxy, with a compound of the general formula III



III

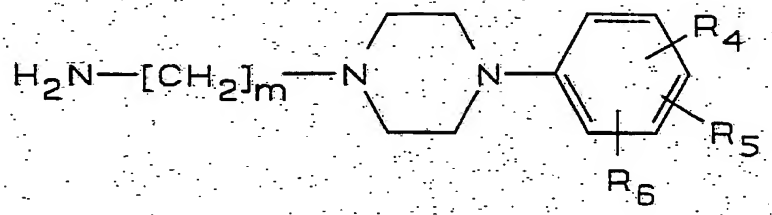
wherein R_4, R_5 and R_6 are as defined above in the presence of a suitable reducing agent such as sodium cyanoborohydride or lithium aluminium hydride in a direct or stepwise manner.

D) Reaction of a compound of the general formula VI



VI

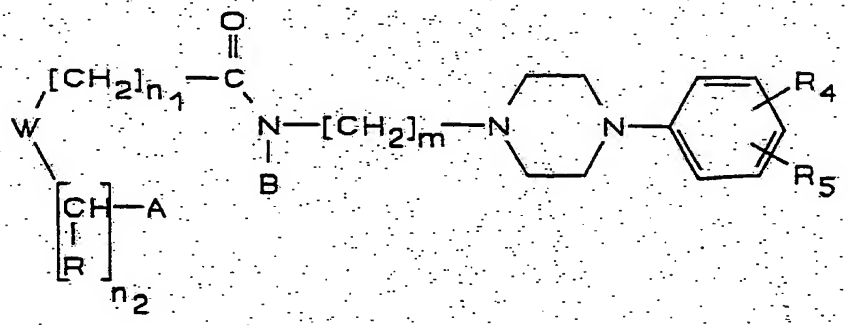
wherein W, n_1, n_2, and A are as defined above, and T independently or together with A represents a suitable derivative of an aliphatic, cycloaliphatic, aromatic or heterocyclic acid or acid derivative, such as a halide, an ester, an imide, an anhydride, or other acid activating group, with a compound of the general formula VII



VII

wherein m, R_4, R_5 and R_6 are as defined above, in a suitable solvent such as dichloromethane, chloroform, toluene, acetic acid, or tetrahydrofuran or neat at ambient or elevated temperature for a prolonged time.

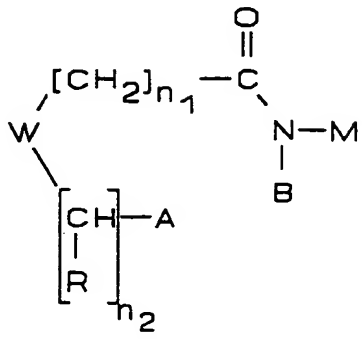
E) Reaction of a compound of the general formula VIII



VIII

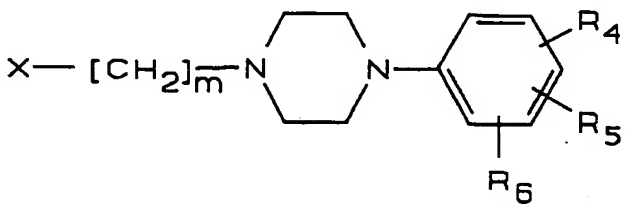
wherein R, m, R_4, W, A, B, n_1 and n_2 are as defined above and R_5 is H, halogen, or CF_3 with a suitable halogenating reagent such as sulfuryl chloride, or bromine in a suitable solvent such as chloroform or dioxane.

F) Reaction of a compound of the general formula IX



IX

wherein W, n_1 and n_2 are as defined above, A and B together represent a carbonyl group, and M represents a suitable alkali metal such as sodium or potassium, with a compound of the general formula X

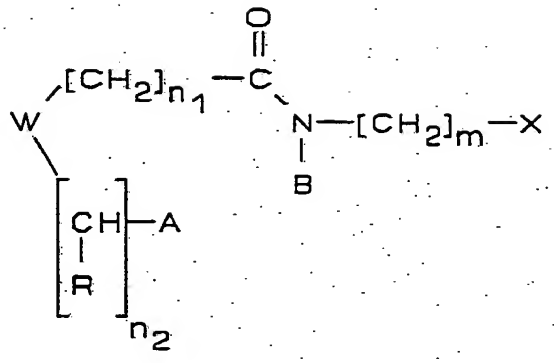


X

wherein X, R_4, R_5 and R_6 are as defined above in a suitable solvent such as DMF, acetonitrile, or DMSO in the presence of a base such as triethylamine, sodium hydroxide, or potassium carbonate at ambient or higher temperature for a prolonged time.

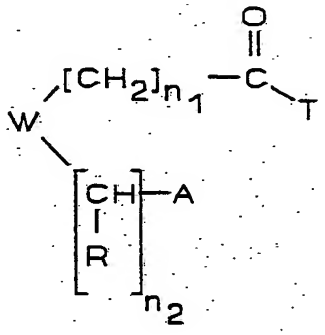
Intermediates

A compound of the general formula II



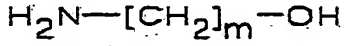
II

wherein R, m, W, A, B, n_1, n_2 and X are as defined above, can be prepared by reacting a compound of the general formula VI



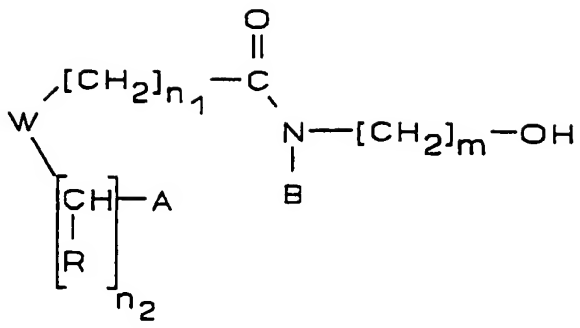
VI

wherein W, n_1, n_2, and A are as defined above, and T independently or together with A represents a suitable derivative of an aliphatic, cycloaliphatic, aromatic or heterocyclic acid or acid derivative, such as a halide, an ester, an imide, an anhydride, or other acid activating group, with a compound of the general formula XI



XI

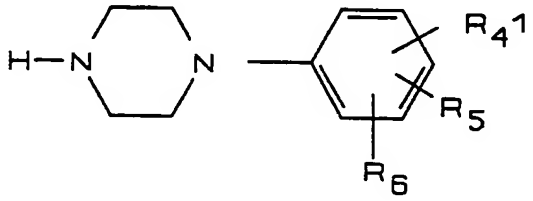
wherein m is as defined above, in a suitable solvent such as dichloromethane, chloroform, toluene, acetic acid, or tetrahydrofuran or neat at ambient or elevated temperature for a prolonged time, and subsequently reacting the intermediate of the general formula XII



XII

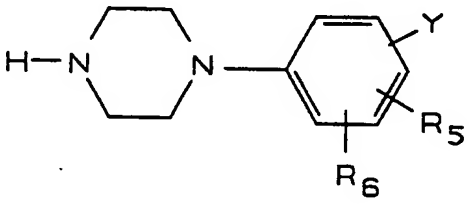
wherein R, m, W, A, B, n_1 and n_2 are as defined above, with a suitable halogenating agent such as thionyl chloride, phosgene, oxalyl chloride, or phosphorous tribromide, or with a suitable sulfonating agent such as tosyl chloride or other arylsulfonyl chloride or alkylsulfonyl chloride.

A compound of the general formula III^1



III^1

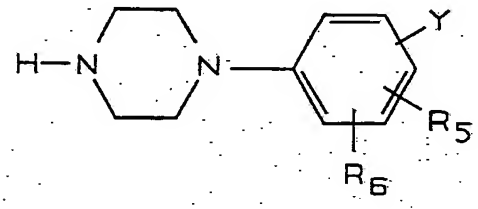
wherein R_4^1, R_5 and R_6 are as defined above can be prepared from a compound of the general formula XIII



XIII

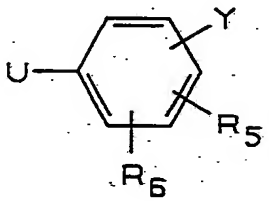
wherein Y, R_5 and R_6 are as defined above in analogy with method B.

A compound of the general formula XIII



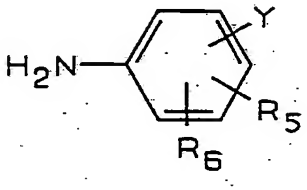
XIII

wherein R_5 and R_6 are as defined above and Y is NO_2 can be prepared by reacting a compound of the general formula XIV



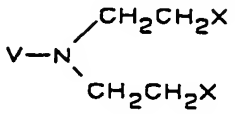
XIV

wherein R_5 and R_6 are as defined above, Y is NO_2 and U is a halogen, with piperazine or a suitably monosubstituted piperazine, where the substituent is easily removeable, such as a benzyl or an ethoxycarbonyl group,
or by reacting a compound of the general formula XV



XV

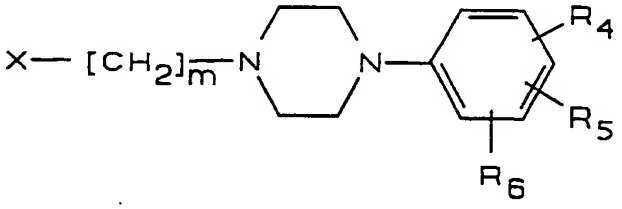
wherein R_5 and R_6 are as defined above and Y is NO_2, with a compound of the general formula XVI



XVI

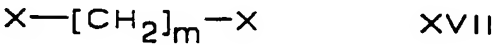
wherein X is as defined above and V is hydrogen or an easily removable group such as benzyl or ethoxycarbonyl.

A compound of the general formula X



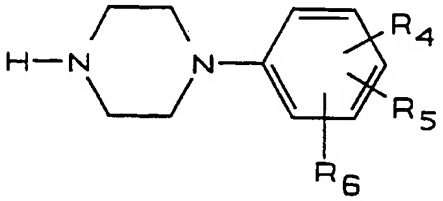
X

wherein X, m, R_4, R_5 and R_6 are as defined above, can be prepared by reacting a compound of the general formula XVII



XVII

wherein X and m are as defined above,
with a compound of the general formula III



III

wherein R_4, R_5 and R_6 are as defined above, under suitable reaction conditions analogous to method A.

Pharmaceutical formulations

According to the present invention the compounds of the formula I will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic, acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulfate, sulfamate, citrate, tartrate, oxalate and the like in association with a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99 % by weight of the preparation, more specifically between 0.5 and 20 % by weight for preparations intended for injection and between 0.2 and 50 % by weight for preparations suitable for oral administration.

To produce pharmaceutical formulations containing a compound of the formula I in the form of dosage units for oral application the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer well known in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents or in

water. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the above mentioned excipients for tablets e.g. saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

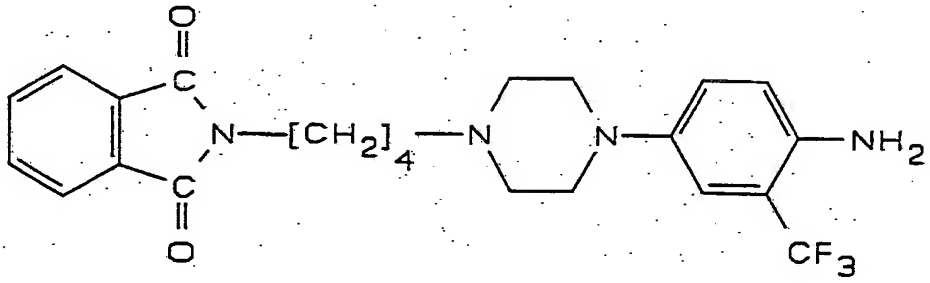
Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing from about 0.2 % to about 20 % by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol, and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent or other excipients well known in the art.

Solutions for parenteral applications can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5 % to about 10 % by weight. These solutions may also contain stabilizing

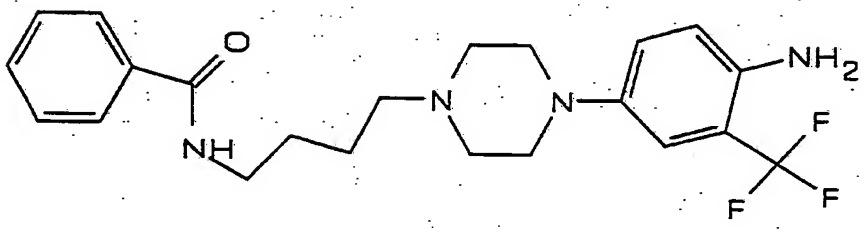
agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are 50 - 500 mg by oral administration and up to 100 mg via parenteral administration.

It is especially preferred to administer a compound of the formula



or



EXAMPLES

Example 1 (Method A)

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)piperazine dihydrochloride

A mixture of 3.18 g (0.01 mol) of 4-amino-3-trifluoromethylphenylpiperazine, a catalytic amount of KI, 4.1 g (0.03 mol) of potassium carbonate and 3.0 g (0.01 mol) of N-(4-bromobutyl)phthalimide in 25 ml of DMF was stirred at 100°C overnight. After addition of 500 ml of water, the mixture was extracted with ether. The extract was washed with water and extracted with dilute hydrochloric acid. The water layer was separated, made alkaline with sodium hydroxide and again extracted with ether. The extract was dried (Na_2SO_4) and acidified with hydrogen chloride in ether. The yielded precipitate was filtered off and recrystallized from ethanol-ether.
Yield 3.0 g (58%).
M.p. 226-227°C.

In an analogous way the following compounds (2-12) were prepared:

Example 2

1-(4-Amino-3-trifluoromethylphenyl)-4-(3-phthalimido-1-propyl)piperazine dihydrochloride.

M.p. 167-169°C.

Example 3

1-(4-Amino-3-trifluoromethylphenyl)-4-[5-(3-methoxyphthalimido)-1-pentyl]piperazine oxalate

M.p. 114-118°C.

Example 4

1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(4-chlorophthalimido)-1-butyl]piperazine dihydrochloride.

M.p. 203-204°C.

Example 5

1-(4-Amino-3-trifluoromethylphenyl)-4-(5-phthalimido-1-pentyl)piperazine trihydrochloride.

M.p. 109-113°C.

Example 6

1-(4-Amino-3,5-dichlorophenyl)-4-(4-phthalimido-1-butyl)piperazine

M.p. 116-119°C.

Example 7

1-(4-Amino-3-trifluoromethylphenyl)-4-[3-(1,8-naphthalimido)-1-propyl]piperazine

M.p. 156-158°C.

Example 8

1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(3,3-dimethylglutarimido)-1-butyl]piperazine dihydrochloride

M.p. 235-236°C.

Example 9

1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(3,3-tetramethyleneglutarimido)-1-butyl]piperazine dihydrochloride

M.p. 243-245°C.

Example 10

1-(4-Amino-3-trifluoromethylphenyl)-4-[5-(3-phenylglutarimido)-1-pentyl]piperazine hydrochloride

M.p. 136-140°C.

Example 11

1-(3-Amino-4-chlorophenyl)-4-[5-(2-furanecarboxamido)-1-pentyl]piperazine oxalate

M.p. 165-170°C.

Example 12

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-cyclohexanecarboxamido-1-butyl)piperazine

M.p. 127-128°C.

Example 13 (Method B)

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)piperazine acetate.

The product from example 38, (9.53 g, 20 mmol), dissolved in 100 ml ethanol and 50 ml acetic acid was hydrogenated with Pd/C (1.0 g) as catalyst for 5 h. The mixture was filtered, the solvent evaporated and the residue crystallized from diisopropylether and ethanol to yield 10.0 g of the title product.
M.p. 101-103°C.

In an analogous way the following compounds (examples 14-24) were prepared:

Example 14

1-(4-Amino-3-trifluoromethylphenyl)-4-(6-phthalimido-1-hexyl)piperazine acetate

M.p. 125-127°C.

Example 15

1-(4-Amino-3-trifluoromethylphenyl)-4-(8-phthalimido-1-octyl)piperazine acetate

M.p. 94-96°C.

Example 16

1-(3-Amino-4-chlorophenyl)-4-(4-phthalimido-1-butyl)-piperazine acetate.

M.p. 159-162°C.

Example 17

1-(3-Amino-4-chlorophenyl)-4-(5-phthalimido-1-pentyl)-piperazine acetate.

M.p. 149-150°C.

Example 18

1-(4-Amino-3-methylphenyl)-4-(4-phthalimido-1-butyl)-piperazine acetate.

M.p. 123-126°C.

Example 19

1-(3-Amino-4-chlorophenyl)-4-[4-(3,3-tetramethylene-glutarimido)-1-butyl]piperazine

M.p. 133-136°C.

Example 20

1-(4-Amino-3-trifluoromethylphenyl)-4-[6-(3-phenoxy-benzamido)-1-hexyl]piperazine acetate

M.p. 128-131°C.

Example 21

1-(4-Amino-3-trifluoromethylphenyl)-4-(6-cyclohexane-carboxamido-1-hexyl)piperazine dihydrochloride

M.p. 112-115°C.

Example 22

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-adamantane-carboxamido-1-butyl)piperazine dihydrochloride

M.p. 123-125°C.

Example 23

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-adamantane-acetamido-1-butyl)piperazine

M.p. 115-116°C.

Example 24

1-(4-Amino-3-trifluoromethylphenyl)-4-(6-adamantane-carboxamido-1-hexyl)piperazine

^{1}H NMR (CDCl3) d 7.00 (s, 1 H), 6.96 (dd, 1 H), 6.70 (d, 1 H), 5.57 (bs, 1 H), 3.26 (bs, 2 H), 3.24 (m, 2 H), 3.08 (m, 4 H), 2.61 (m, 4 H), 2.39 (m, 2 H), 2.04 (bs, 3 H), 1.84 (bs, 6 H), 1.71 (bs, 6H), 1.52 (m, 4 H), 1.34 (m, 4 H).

Example 25 (Method B)

1-(4-Amino-2-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)piperazine dihydrochloride.

To a mixture of 1-(4-nitro-2-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)-piperazine (7.8 g, 0.01 mol) in 200 ml ethanol and 60 ml water, 11.2 g of sodium dithionite was added in portions while stirring and heating at 100°C. The mixture was heated under reflux for 1 h and the ethanol was evaporated. The residual water solution

was made basic with NaOH and extracted with ether. The extract was washed with water, dried and the ether was evaporated. The yielded oil was dissolved in 100 ml dry ether and the dihydrochloride was precipitated by the addition of hydrogen chloride in ether. The salt was recrystallized from ethanol-ether to give 2.3 g (44 %) of the target compound.
M.p. 243 -244°C.

Example 26 (Method B)

1-(4-Diethylamino-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)-piperazine

The product from Example 13 (1.0 g, 2 mmol), dissolved in 5 ml acetic acid, was added to a mixture of sodium borohydride (304 mg, 8 mmol) and 20 ml toluene. The mixture was heated for 6 h at 80°C, cooled and added to 50 ml water and 50 ml ether and made alkaline with 2 M sodium hydroxide. The organic phase was dried and evaporated. The residue was recrystallized from hexane to yield 440 mg of the target product.
M.p. 70 - 71°C.

Example 27 (Method B)

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)-piperazine.

4-(4-Acetamino-3-trifluoromethylphenyl)-1-(4-phthalimido-1- butyl)-piperazine (4.9 mg, 0.01 mmol), dissolved in 2 ml ethanol and 0.2 ml 2 M hydrochloric acid, was heated for 5 h at 80°C. The solvent was removed and the residue was shown by gas chromatography to be identical with the product in example 1.

Example 28 (Method C)

4-(4-Amino-3-trifluoromethylphenyl)-1-(4-phthalimido-1-butyl)-piperazine

To a refluxing solution of 4-phthalimido-1-butanal (0.713 g 3.25 mmol) and N-(4-amino-3-trifluoromethylphenyl)-piperazine (0.804 g, 3.25 mmol) in $CHCl_3$ (10 ml) was added dropwise 98% formic acid in $CHCl_3$ (10 ml) in 20 min. The solution was heated under reflux for 2 h. The solvent was removed and the residue purified by chromatography and shown by thin layer chromatography and gas chromatography to be identical to the product in example 1.

Example 29 (Method D)

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)piperazine

4-(4-Amino-3-trifluoromethylphenyl)-1-(4-aminobutyl)-pipera zine(32 mg, 0.1 mmol) and phthalic anhydride (30 mg, 0.2 mmol) dissolved in 1 ml acetic acid were stirred at 75°C for 3 hours. The solvent was removed and the residue was shown by gas chromatography and thin layer chromatography to be identical with the product in example 1.

Example 30 (Method D)

1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(5-bromo-2,3-dimethoxybenzamido)-1-butyl]piperazine dioxalate

The product from example 1 (3.3 g, 6.4 mmol) was dissolved in 60 ml ethanol, made alkaline with 2 M NaOH, and the base was heated with hydrazine hydrate (2.0 ml) at 75°C for 3.5 h. After cooling, the solution was

acidified with 27 ml 2 M HCl and evaporated. The residue was dissolved in 75 ml H_2O and 75 ml ether. The aqueous phase was made alkaline and extracted with chloroform. The solvent was evaporated to yield crude 1-(4-aminobutyl)-4-(4-amino-3-trifluoromethylphenyl)-piperazine. A solution of 5-bromo-2,3-dimethoxybenzoic acid (0.52 g, 2.0 mmol) in 10 ml toluene, thionylchloride (2 ml, 23 mmol), and a few drops of DMF was heated at 60°C for 3 h. The solvent was evaporated and the residue was dissolved in 15 ml of dichloromethane and evaporated again. The residual acyl chloride was dissolved in 15 ml dichloromethane and a solution of the crude amin from above (0.51 g, 1.6 mmol) and triethylamine (0.45 g, 3.2 mmol) in 10 ml dichloromethane was added with cooling. After stirring overnight the solvent was evaporated and the residue was partitioned between dil. HCl and ether. The organic phase was extracted with water and the combined water phases were made alkaline and extracted repeatedly with chloroform. Drying (Na_2SO_4) and evaporation gave 0.57 g of the product as an oil. The base was dissolved in aceton and treated with oxalic acid affording 0.95 g of the title product.
M.p. 174-175°C.

In an analogous way the following compounds (examples 31-34) were prepared:

Example 31

1-(4-Amino-3-trifluoromethylphenyl)-4-(4-benzamido-1-butyl)piperazine

M.p. 117-120°C.

Example 32

1-(4-Amino-3-trifluoromethylphenyl)-4-[5-(5-bromo-2,3-dimethoxybenzamido)-1-pentyl]piperazine dioxalate

M.p. 151-154°C.

Example 33

1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(2-norbornanecarboxamido)-1-butyl]piperazine hydrochloride

M.p. 77-80°C.

Example 34

(R,endo)-1-(4-Amino-3-trifluoromethylphenyl)-4-[4-(2-norbornanecarboxamido)-1-butyl]piperazine hydrochloride

M.p. 142-146°C.

Example 35 (Method E)

1-(4-Amino-5-bromo-3-trifluoromethylphenyl)-4-(4-phthalimido-1-butyl)piperazine oxalate

The product in Example 13 (1.0 g, 2 mmol) was dissolved in 20 ml dioxane and 5 ml methanol. Bromine (350 mg, 2.2 mmol) dissolved in 3 ml dioxane was added and the mixture stirred at ambient temperature for 5 hours, the solvent evaporated, the residue made alkaline with 2 M aqueous NaOH and extracted with methylene chloride. The solvent was removed and the residue dissolved in diisopropyl ether and a precipitate of the title compound was obtained with oxalic acid dissolved in ethanol.
M.p. 172-175°C.

Example 36 (intermediate, compound II)

N-(5-Bromopentyl)-3-methoxyphthalimide

3-Methoxyphthalic anhydride (3.0 g, 16.8 mmol) and 5-amino-1-pentanol(1.7 g, 16.8 mmol) were mixed and heated to 120°C for 2 h. After cooling phosphorus tribromide (3.5 g, 13 mmol) was added and the mixture heated to 110°C for 2 h and poured into ice, extracted with ethyl acetate and the organic phase was separated, dried and the solvent evaporated. The residue was crystallized from ethyl acetate/hexane.
M.p. 65-67°C.

Example 37 (intermediate compound II)

N-(5-Tosyloxypentyl)-5-bromo-2,3-dimethoxybenzamide

A solution of 5-bromo-2,3-dimethoxybenzoic acid (1.56 g, 6.0 mmol) in 25 ml toluene, thionyl chloride (6 ml, 70 mmol), and a few drops of DMF was heated at 60°C for 3 h. The solvent was evaporated, and the residue dissolved in 20 ml dichloromethane and evaporated again. The residual acid chloride was dissolved in 20 ml dichloromethane and added to a solution of 5-aminopentanol (1.8 g, 18 mmol) and triethylamine (4 ml, 28 mmol) in 30 ml dichloromethane at -35°C and the temperature allowed to rise to 0°C in 4 h. The solution was washed with dilute HCl, the organic phase separated, and the solvent removed to yield 2.2 g of a crude oil. This oil was dissolved in 20 ml dichloromethane, triethylamine (4 ml, 28 mmol) and tosylchloride (1.33 g, 7 mmol) were added, and the mixture was stirred at ambient temperature overnight. Ethyl ether (100 ml) was added and the organic phase washed with sodium carbonate solution and water. After drying, the organic solvent was evaporated to yield 2.7 g (5.5 mmol) of the title product as an oil.

^{1}H NMR($CDCL_3$) d 7.9 (bs, 1 H), 7.81 (d, 1 H), 7.77 (d, 2 H), 7.34 (d, 2 H), 7.13 (d, 1 H), 4.03 (t, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.42 (q, 2 H), 2.44 (s, 3 H), 1.73-1.40 (m, 6 H).

Example 38 (intermediate compound IV)

1-(4-Nitro-3-trifluoromethylphenyl)-4-(phthalimido-1-butyl)piperazine

The compound from example 39 (8.5 g, 30 mmol), 4-bromobutylphthalimide (11.1 g, 40 mmol), potassium carbonate (5.0 g, 36 mmol) and a catalytic amount of potassium iodide were warmed to 90°C in 80 ml DMF for 6 h. The mixture was poured into 500 ml water and extracted with methylene chloride. The organic phase was dried, the solvent evaporated and the residue triturated with ethanol/diisopropyl ether to yield a yellow, crystalline product.
M.p. 152-154°C.

Example 39 (intermediate compound XIII)

1-(4-Nitro-3-trifluoromethylphenyl)piperazine

A mixture of 22,4 g (0.1 mol) of 4-nitro-3-trifluoro-methyl-1-chlorobenzene, 50,0 g (0.58 mol) of anhydrous piperazine and a catalytical amount of KI in 80 ml of 1-propanol was stirred and heated at 100°C overnight. After cooling, 1 l of ice-water was added with stirring. The yielded precipitate was filtered off, washed with water and dried.
Yield 26.6 g (94%). M.p. 81-83°C.

Example 40 (intermediate compound XIII)

4-Amino-2,6-dichlorophenylpiperazine

2,6-Dichloro-4-nitroaniline (10.4 g, 50 mmol), dissolved in 100 ml methanol and 10 ml 2 M HCl, was hydrogenated with platinum on carbon as catalyst at NTP in 8 h. The catalyst was filtered off and the solvent removed. The residue was dissolved in ether and made alkaline to yield 5.1 g (29 mmol) of a grey crystalline powder. This product was reacted with bis-(2-chloroethyl)amine hydrochloride (5.4 g, 30 mmol) with heating to 100°C in n-butanol with 3x1 g sodium carbonate (30 mmol) for 26 h. The solvent was evaporated, the residue taken up in ether and made alkaline to yield 3.4 g (48 %) of product as an oil.

^{1}H NMR($CDCL_3$) d 6.82 (s, 2 H), 4.10 (s, 2 H), 3.02 (m, 8 H), 1.82 (s, 1 H).

Pharmaceutical preparations

The following examples illustrate suitable pharmaceutical compositions to be used in the method of the invention. For the preparation of tablets the following compositions can be made.

Composition 1

Compound according to Example 1		50 g
Lactose	85 g	
Potato starch		40 g
Polyvinylpyrrolidone		5 g
Microcrystalline cellulose	18 g	
Magnesium stearate		2 g

Composition 2

Compound according to Example 1	100 g
Lactose	90 g
Potato starch	50 g
Polyvinylpyrrolidone	5 g
Microcrystalline cellulose	23 g
Magnesium stearate	2 g

From the above compositions 1 000 tablets can be made, containing 50 mg and 100 mg of active substance, respectively. If desired, the obtained tablets can be film coated with e.g. hydroxypropyl methyl cellulose in an organic solvent or using water.

Pharmacology

It is generally accepted that drugs that bind to dopamine D2 receptors and are antagonists at these receptors will be clinically effective as antipsychotic agents (for example in schizophrenia). It is also believed that a serotoninergic (5HT1A) receptor affinity as an agonist can be a useful property by reducing the incidence of extrapyramidal side effects and by increasing the efficacy of the substance in psychoses. These substances by having a certain ratio of D2 and 5HT1A binding will retain an antipsychotic effect at the same time as having a reduced incidence of side effects and improved efficacy.

Table 1 illustrates the binding affinities (K_i values, nM) of several of the compounds at dopamine (D2) and serotonin (5HT1A) receptors and the ratios D2/5HT1A.

The pharmacological methods are described below.

D2 Receptor Binding Assay

Tissue preparation: The rats are decapitated and the striata dissected out on ice. The tissue is homogenized at 0°C in 20 ml 0.05 M Tris-HCl buffer pH 7.7, using a Branson B30 sonifier. The homogenate is centrifuged at 4°C for 10 minutes at 48000 g, in a Sorvall RC-5B Refrigerated Superspeed Centrifuge. The pellet is resuspended and recentrifuged. The final pellet is resuspended in incubation buffer (0.05 M Tris-HCl pH 7.6 containing 0.1% ascorbic acid, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 10 µM pargylin), to a final concentration of 2.5 mg wet weight/0.5 ml. The homogenate is preincubated for 10 min at 37°C.

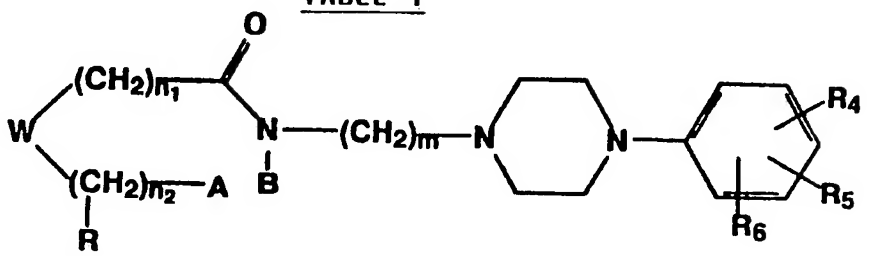
Receptor binding assay: Various concentrations of the test compound, the radioligand (1nM ^{3}H-Raclopride) and the homogenate are incubated for 60 min at room temperature. Non-specific binding is determined by the addition of 1 µM (+)-Butaclamol. The incubation is terminated by rapid filtration through glass fiber paper (Whatman GF/B) and subsequent washing with cold incubation buffer, using a cell harvester equipment. The radioactivity of the filters is measured in a Packard 2200CA liquid scintillation counter. Data is analyzed by non-linear regression using the LIGAND program, and presented as Ki values.

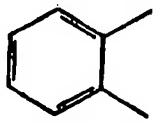
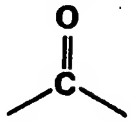
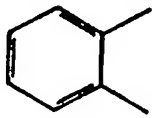
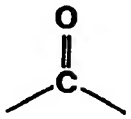
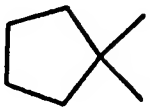
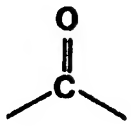
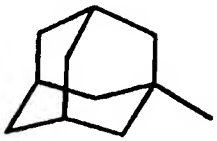
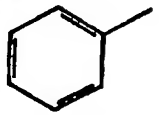
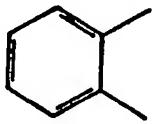
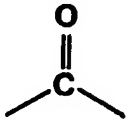
5-HT_{1A} Receptor binding Assay

Tissue preparation. Cerebral cortex + hippocampus from each rat was dissected and homogenized in 15 ml ice-cold 50mM Tris-HCl buffer 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5 with an Ultra-Turrax (Janke & Kunkel, Staufen, FRG) for ten s. After centrifugation for 12.5 min at 17,000 rpm (39,800 x g in a Beckman centrifuge with a chilled JA-17 rotor (Beckman, Palo Alto, CA, USA),

the pellets were resuspended in the same buffer and homogenization and centrifugation repeated. To each pellet 5 ml ice-cold 0.32 M sucrose were added and homogenized for 5 sec. These samples were kept frozen at -70°C. When used they were diluted with the buffer to 8 mg tissue/ml and homogenized for 10 sec. The tissue homogenates were incubated for ten min at 37°C and then supplied with 10 µM pargyline followed by reincubation for 10 min. The binding assay followed that described by Peroutka, J. Neurochem. 47, 529-540, (1986). The incubation mixture (2 ml) contained ^{3}H-8-OH-DPAT (0.25 to 8 nM), 5 mg/ml tissue homogenate in 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5. Six different concentrations of ^{3}H-8-OH-DPAT were analyzed. Binding experiments were started by the addition of tissue homogenate and followed by incubation at 37°C for ten min. The incubation mixtures were filtered through Whatman GF/B glass filters with a Brandel Cell Harvester (Gaithersburgh, MD, USA). The filters were washed twice with 5 ml ice-cold 50 mM Tris-HCl buffer, pH 7.5, and counted with 5 ml Ultima Gold™ (Packard) in a Beckman LS 3801 scintillation counter. Non-specific binding was measured by the addition of 10 µM 5-HT to the reaction mixture. The binding data were processed by non-linear least squares computer analysis (Munson and Rodbard, Anal. Biochem. 107, 220-239, (1980). Data were presented as K_i values (nM).

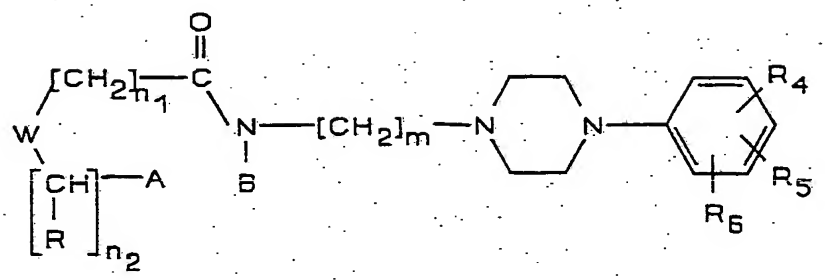
TABLE 1



Ex. no.	R	W	n1	n2	A	B	m	R4	R5	R6	Binding K_i (nM) D_2	Binding K_i (nM) 5-HT1A	Ratio D_2/5HT1A
1	H		0	0			4	4-NH_2	3-CF_3	H	9	10	1
8	H		0	0			4	3-NH_2	4-Cl	H	14	80	0.17
19	H		1	1			4	3-NH_2	4-Cl	H	13	220	0.06
22	H		0	0	H	H	4	4-NH_2	3-CF_3	H	42	31	1.4
31	H		0	0	H	H	4	4-NH_2	3-CF_3	H	9	60	0.15
NAN 190	H		0	0			4	H	2-MeO	H	19	2	10

CLAIMS

1. A compound of the general formula



I

or pharmaceutically accetable salts thereof, wherein

R is a hydrogen atom or a phenyl group,

m is an integer 3 to 8,

R_4 is situated in the meta or para position of the ring and represents an NO_2-group or a group NR_7R_8 wherein R_7 and R_8 are the same or different and each represents a hydrogen atom or an alkyl group having 1-3 carbon atoms,

R_5 is situated in the ortho, meta or para position and represents an hydrogen atom, a halogen atom or CF_3,

R_6 is situated in the ortho, meta or para position and represents a halogen atom or CF_3,

W is an optionally substituted aromatic ring(s), a heterocyclic ring, a carbocyclic ring(s), or an optionally substituted methylene group,

A is a hydrogen atom, a hydroxy group, a halogen atom, CF_3, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group,

B is a hydrogen atom, or

A and B together constitute a carbonyl group,

n_1 is 0 or 1, and

n_2 is 0 or 1,

in racemic or optically active form, or as a mixture of diastereomers, provided that

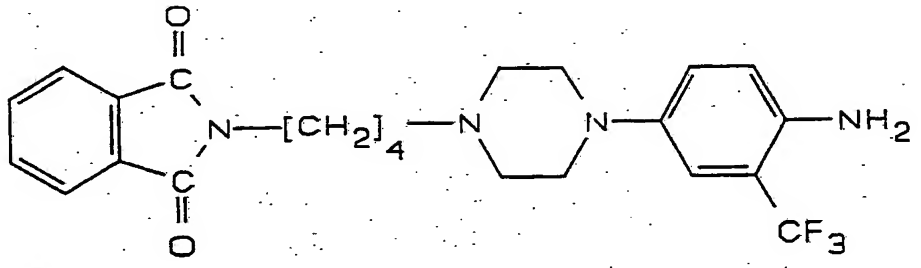
1) when W is an optionally substituted aromatic ring(s) then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A is a hydrogen atom, a halogen atom, CF_3, a hydroxy group, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group, and
B is a hydrogen atom or
A and B together constitute a carbonyl group,

2) when W is a carbocyclic ring(s) or a heterocyclic ring then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 is 0 or 1,

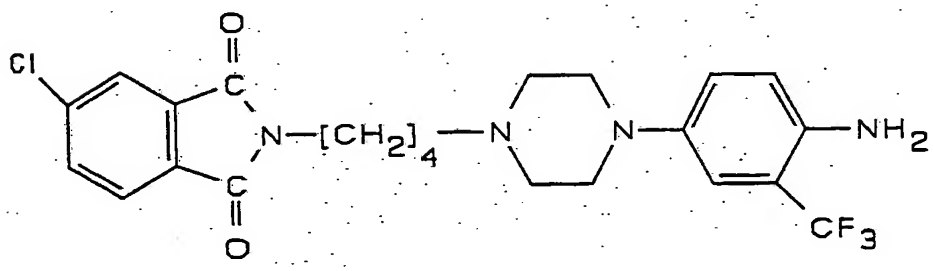
n_2 is 0 or 1,
A and B are hydrogen atoms or
A and B together constitute a carbonyl group,

3) when W is an optionally substituted methylene group then
R, m, R_4, R_5, and R_6 are as defined above,
n_1 and n_2 are 1 or
n_1 is 1 and n_2 is 0 or
n_1 is 0 and n_2 is 1,
A and B together constitute a carbonyl group,

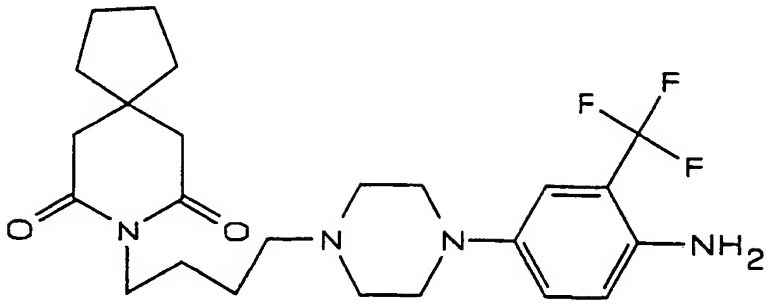
2. A compound according to claim 1 having the formula



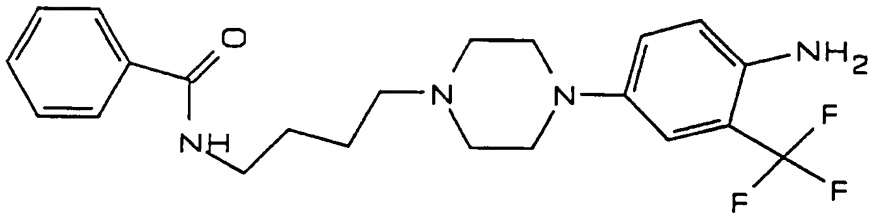
or



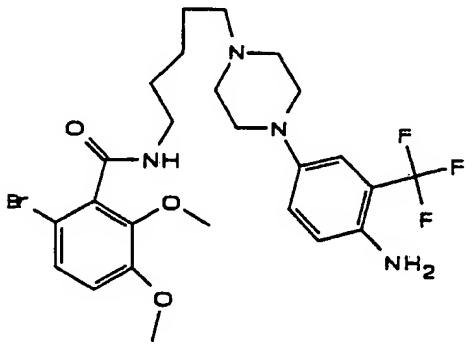
or

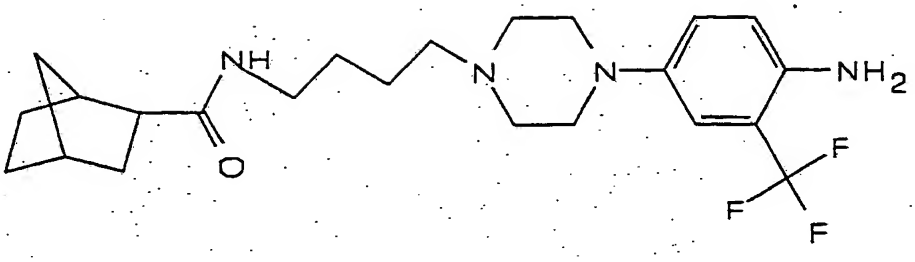


or

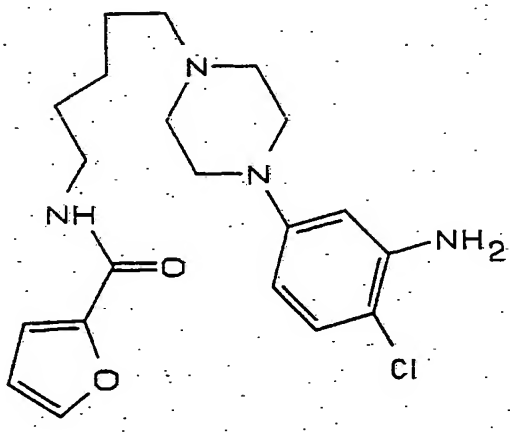


or

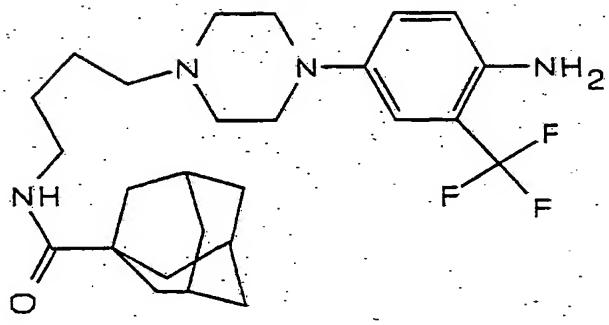




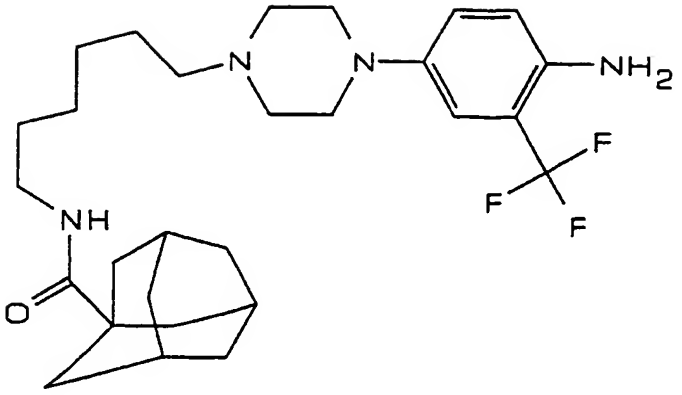
or



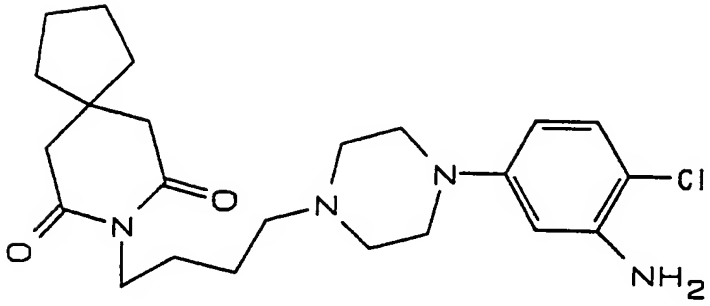
or



or



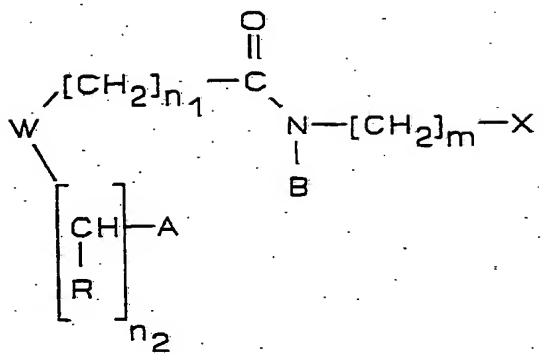
or



3. A process for the preparation of a compound of the general formula I as defined in claim 1, characterized by

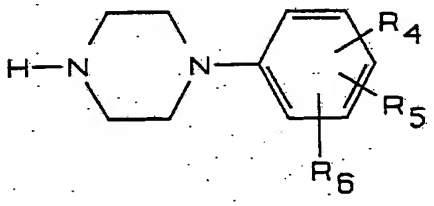
A) reaction of a compound of the general formula II

50



II

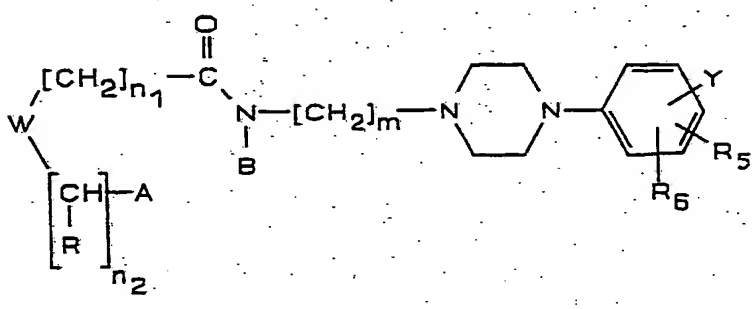
wherein R, m, W, A, B, n_1 and n_2 are as defined in claim 1 and X is a leaving group with a compound of the general formula III



III

wherein R_4, R_5 and R_6 are as defined in claim 1, or

B) conversion of a compound of the general formula IV

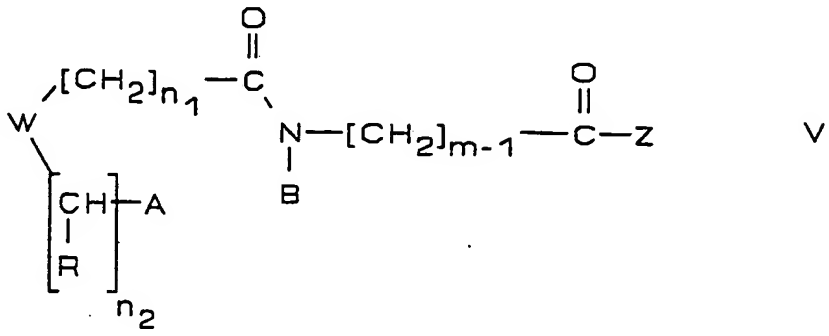


IV

wherein R, m, R_5, R_6, W, A, B, n_1 and n_2 are as defined in claim 1 and Y is situated in the meta or para position and represents a group which can be transformed to a

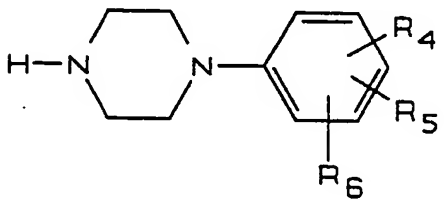
group R_4^1, where R_4^1 is situated in the meta or para position of the ring and represents a group NR_7R_8 as defined in claim 1, or

C) reaction of a compound of the general formula V



V

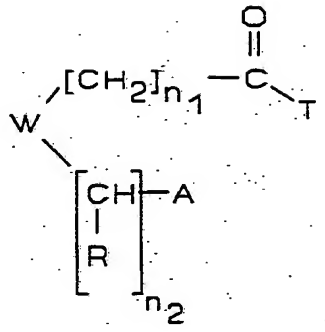
wherein R, m, W, A, B, n_1 and n_2 are as defined in claim 1 and Z is hydrogen, hydroxy, halogen, or alkoxy, with a compound of the general formula III



III

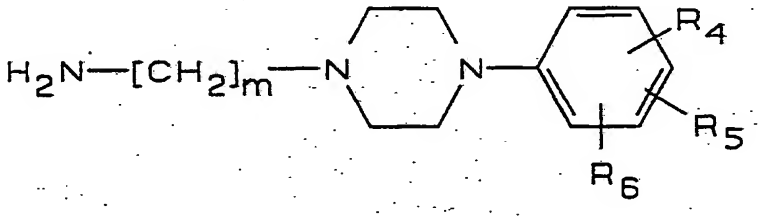
wherein R_4, R_5 and R_6 are as defined in claim 1, or

D) reaction of a compound of the general formula VI



VI

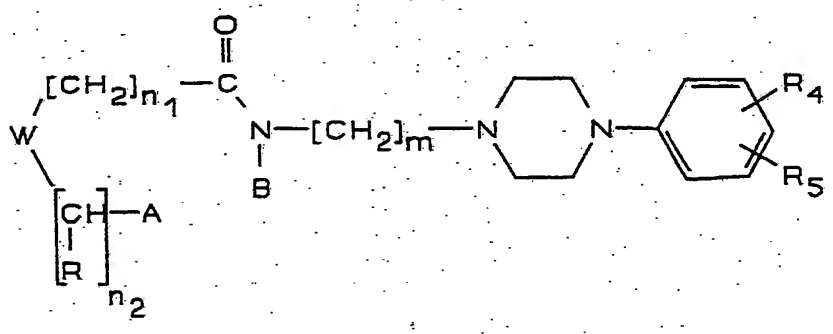
wherein W, n_1, n_2, and A are as defined in claim 1, and T independently or together with A represents a suitable derivative of an aliphatic, cycloaliphatic, aromatic or heterocyclic acid or acid derivative with a compound of the general formula VII



VII

wherein m, R_4, R_5 and R_6 are as defined in claim 1, or

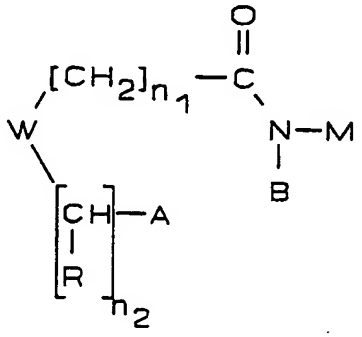
E) reaction of a compound of the general formula VIII



VIII

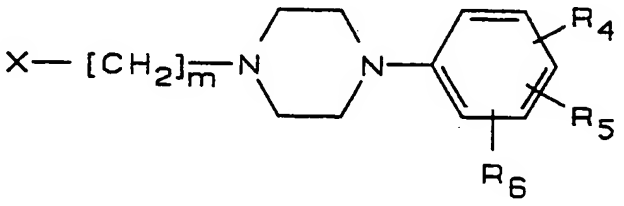
wherein R, m, R_4, W, A, B, n_1 and n_2 are as defined in claim 1 and R_5 is H,halogen, or CF_3 with a suitable halogenating reagent or

F) reaction of a compound of the general formula IX



IX

wherein W, n_1 and n_2 are as defined in claim 1, A and B together represent a carbonyl group, and M represents an alkali metal with a compound of the general formula X

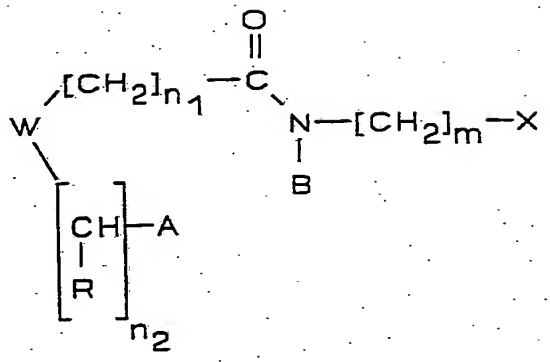


X

wherein X, R_4, R_5 and R_6 are as defined in claim 1, whereafter, if so desired the compound obtained by any of the processes A)-F) is converted to a pharmaceutically acceptable salt thereof.

4. A process according to claim 3 characterized in that compound according to claim 2 is prepared.

5. A compound of the formula II



II

R is a hydrogen atom or a phenyl group,

m is an integer 3 to 8,

W is an optionally substituted aromatic ring(s), a heterocyclic ring, a carbocyclic ring(s), or an optionally substituted methylene group,

A is a hydrogen atom, a hydroxy group, a halogen atom, CF_3, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group,

B is a hydrogen atom, or

A and B together constitute a carbonyl group,

n_1 is 0 or 1, and

n_2 is 0 or 1,

in racemic or optically active form, or as a mixture of diastereomers, provided that

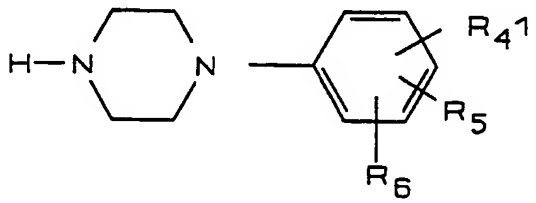
1) when W is an optionally substituted aromatic ring(s) then

R and m, are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A is a hydrogen atom, a halogen atom, CF_3, a hydroxy group, an alkyl group having 1-3 carbon atoms, an alkoxy group having 1-3 carbon atoms, a phenyl group, or a phenoxy group, and
B is a hydrogen atom or
A and B together constitute a carbonyl group,

2) when W is a carbocyclic ring(s) or a heterocyclic ring then
R, and m, are as defined above,
n_1 is 0 or 1,
n_2 is 0 or 1,
A and B are hydrogen atoms or
A and B together constitute a carbonyl group,

3) when W is an optionally substituted methylene group then
R, and m, are as defined above,
n_1 and n_2 are 1 or
n_1 is 1 and n_2 is 0 or
n_1 is 0 and n_2 is 1,
A and B together constitute a carbonyl group.

6. A compound of the formula III^1



III^1

wherein $R_4$1 is situated in the meta or para position of the ring and represents a group NR_7R_8 wherein R_7 and R_8

are the same or different and each represents a hydrogen atom or an alkyl group having 1-3 carbon atoms,

R_5 is situated in the ortho, meta or para position and represents a hydrogen atom, a halogen atom, or CF_3,

R_6 is situated in the ortho, meta or para position and represents a halogen atom or CF_3.

7. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1-2.

8. A pharmaceutical preparation according to claim 7 in dosage unit form.

9. A pharmaceutical preparation according to claims 8-9 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

10. A compound according to any of claims 1-2 for use as a therapeutically active substance.

11. Use of a compound according to any of claims 1-2 for the preparation of medicaments with effect against mental disturbances.

12. A method for the treatment of mental disturbances in mammals, including man, characterized by the administration to a host in need of such treatment of an effective amount of a compound according to any of claims 1-2.

13. Compounds and processes and intermediates, for their preparation, pharmaceutical compositions containing them, and their use in the treatment of mental disturbances as claimed in claim 1-12 inclusive and substantially as described.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07D 403/06, C07D 401/06, C07D 405/06, C07D 295/073, C07D 295/125, C07D 295/135, C07D 209/48, C07C 309/73, A61K 31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07D, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 34, August 1991, Revathi K. Raghupathi et al, "Analogues of the 5-HT 1A Serotonin Antagonist 1-(2-Methoxy-phenyl)-4-/4-(2-phthalimido)butyl/piperazine with Reduced alfa1-Adrenergic Affinity", page 2633 - page 2638, see especially compounds 1c, 1f and 2a-2c	1-5,7-11
X	J Indian Chem. Soc.,, Volume LVI, October 1979, Samant et al, "Synthesis and Pharmacology of N-(N4-Aryl-N1-Piperaziny lalkyl)Phthalimides: CNS Depressants", page 1002 - page 1005, see page 1004	1-5,7-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 Sept 1993	16 -09- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9109594 (VIRGINIA COMMONWEALTH UNIVERSITY), 11 July 1991 (11.07.91), see especially pages 11-17 and 66-97	1-4,7-11
X	J. Med. Chem., Volume 31, October 1988, Richard A. Glennon et al, "Arylpiperazine Derivatives as High-Affinity 5-HT1A Serotonin Ligands", page 1968 - page 1971, see specially compounds 15-17 and 23-24	1-5,7-11
X	FR, A, 1537901 (LES LABORATOIRES BRUNEAU ET CIE), 30 August 1968 (30.08.68)	1-4,7-11
X	FR Addition 93884 (LES LABORATOIRES BRUNEAU ET CIE), 30 May 1969 (30.05.69)	1-4,7-11
X	GB, A, 1198459 (SHULTON INC.), 15 July 1970 (15.07.70)	1-4,7-11
X	US, A, 3505338 (WILLIAM BLYTHE WRIGHT, JR ET AL), 7 April 1970 (07.04.70)	1-5,7-11
X	US, A, 3940397 (WADE ET AL), 24 February 1976 (24.02.76)	1-5,7-11
X	EP, A1, 0048045 (DUPHAR INTERNATIONAL RESEARCH B.V.), 24 March 1982 (24.03.82), see especially page 3, example II compound 3) and example III compound 2)	1-4,7-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB, A, 2218988 (AMERICAN HOME PRODUCTS CORPORATION), 29 November 1989 (29.11.89), see especially example 8 and 19	1-4,7-11
	--	
P,X	US, A, 5143923 (HRIB ET AL), 1 Sept 1992 (01.09.92), see column 1-4 and exemple 10	1-5,7-11
	--	
P,X	EP, A1, 526434 (BOEHRINGER INGELHEIM ITALIA S.P.A), 3 February 1993 (03.02.93), see especially example 5	1-4,7-11
	--	
X	US, A, 4892943 (ABOU-GHARBIA), 9 January 1990 (09.01.90), see especially example 30-35	1-4,7-11
	--	
X	US, A, 4939137 (RUSSELL ET AL), 3 July 1990 (03.07.90)	1-5,7-11
	--	
X	EP, A2, 212551 (KALI-CHEMIE PHARMA GMBH), 4 March 1987 (04.03.87), see especially compound 3116 and 3117	1-5,7-11
	--	
X	EP, A2, 0376633 (SUNTORY LIMITED), 4 July 1990 (04.07.90), see pages 6-12 and 25-41	1-5,7-11
	--	
X	US, A, 3398151 (YAO HUA WU), 20 August 1968 (20.08.68)	1-5,7-11
	--	
X	US, A, 3558777 (YAO HUA WU), 26 January 1971 (26.01.71)	1-4,7-11
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Med. Chem., Volume 32, August 1989, Richard A. Glennon et al, "N-(Phthalimidoalkyl)Derivatives of Serotonergic Agents: A Common Interaction at 5-HT1A Serotonin Binding Sites?", page 1921 - page 1926, see table II --	1-4,7-11
A	Journal of Pharmaceutical Sciences, Volume 77, No 10, October 1988, Khalid A. Al-Rashood et al, "Antipsychotic Properties of New N-(4-Substituted-1-Piperazinylethyl)- and N-(4-Substituted-1-Piperidinylethyl)-Phthalimides", page 898 - page 901, see table II --	1-4,7-11
X	US, A, 3465080 (WILLIAM BLYTHE WRIGHT JR), 2 Sept 1969 (02.09.69), see exemple 12 --	5
X	US, A, 4361565 (TEMPLE, JR. ET AL), 30 November 1982 (30.11.82), see exemple 1-3 --	5
X	Chemical Abstracts, Volume 80, No 1, 7 January 1974 (07.01.74), (Columbus, Ohio, USA), page 288, THE ABSTRACT No 37015m, FR, A, 2167355, (Carron, Claude L.C. et al) 28 Sept 1973 (28.09.73), see reg.no. 50845-96-0 --	5
X	Chemical Abstracts, Volume 94, No 25, 22 June 1981 (22.06.81), (Columbus, Ohio, USA), Kormendy, Karoly et al, "Aminophthalazinone derivatives. VI. Synthesis of 4-(hydroxyalkylamino)1-(2H)-benzo[g]phthalazinones", page 594, THE ABSTRACT No 208787k, Acta Chim. Acad Sci. Hung. 1980, 105 (3), 175-188, see reg.no. 77766-48-4 --	5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 110, No 5, 30 January 1989 (30.01.89), (Columbus, Ohio, USA), Giardina Dario et al, "Structure-activity relationships in prazosin-related compounds. Effect of replacing a piperazine ring with an alkanediamine moiety on x1-adrenoreceptor blocking activity", page 540, THE ABSTRACT No 38951p, J. Med. Chem. 1989, 32 (1), 50-55, see reg.no. 116784-96-4	5

--

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00295

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-13
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.

2. [X] Claims Nos.: 1,3 and 5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of claims 1,3 and 5 is so broadly formulated that many compounds of a very wide range of structures is included. The search has thus been limited to the compounds considered to be most relevant.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information patent family members

26/08/93

International application No.
PCT/SE 93/00295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9109594	11/07/91	AU-A- 7168491	24/07/91
		EP-A- 0507863	14/10/92
FR-A- 1537901	30/08/68	NONE	
GB-A- 1198459	15/07/70	CH-A- 505836	15/04/71
		DE-A- 1695783	22/04/71
		FR-A- 1570446	13/06/69
		NL-A- 6713798	16/04/68
		US-A- 3488352	06/01/70
		US-A- 3574839	13/04/71
US-A- 3505338	07/04/70	BE-A- 707032	24/05/68
		CH-A- 509311	30/06/71
		CH-A- 509312	30/06/71
		DE-A- 1670007	21/01/71
		GB-A- 1166364	08/10/69
		NL-A- 6715434	27/05/68
US-A- 3940397	24/02/76	CA-A- 1058178	10/07/79
		DE-A- 2551062	26/05/76
		FR-A,B- 2290903	11/06/76
		GB-A- 1507709	19/04/78
EP-A1- 0048045	24/03/82	AU-A- 7502981	18/03/82
		CA-A- 1155116	11/10/83
		JP-A- 57081464	21/05/82
		NL-A- 8005133	01/04/82
GB-A- 2218988	29/11/89	AU-B- 628341	17/09/92
		AU-A- 3502589	30/11/89
		EP-A- 0343961	29/11/89
		JP-A- 2015059	18/01/90
US-A- 5143923	01/09/92	AU-A- 1518792	05/11/92
		EP-A- 0511610	04/11/92
EP-A1- 526434	03/02/93	NONE	
US-A- 4892943	09/01/90	AU-B- 582906	13/04/89
		AU-A- 6364586	30/04/87
		EP-A- 0220873	06/05/87
		GB-A,B- 2181731	29/04/87
US-A- 4939137	03/07/90	NONE	
EP-A2- 212551	04/03/87	NONE	
EP-A2- 0376633	04/07/90	AU-B- 630904	12/11/92
		AU-A- 4726089	05/07/90
		CA-A- 2006792	28/06/90
		JP-A- 2256671	17/10/90
		US-A- 5071845	10/12/91

INTERNATIONAL SEARCH REPORT
Information on patent family members

26/08/93

International application No.
PCT/SE 93/00295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3398151	20/08/68	BE-A- 693497	01/08/67
		CH-A- 494766	15/08/70
		CH-A- 495368	31/08/70
		DE-A- 1695390	24/02/72
		GB-A- 1164503	17/09/69
		NL-A- 6701538	02/08/67
US-A- 3558777	26/01/71	NONE	
US-A- 3465080	02/09/69	NONE	
US-A- 4361565	30/11/82	AU-B- 560667	16/04/87
		AU-A- 9108482	07/07/83
		BE-A- 895505	28/06/83
		CA-A- 1237722	07/06/88
		CH-A,B- 653682	15/01/86
		DE-A,C- 3248138	07/07/83
		FR-A,B- 2518994	01/07/83
		GB-A,B- 2114121	17/08/83
		JP-A- 58118583	14/07/83
		LU-A- 84562	08/09/83
		NL-A- 8204974	18/07/83
		SE-B,C- 449748	18/05/87
		SE-A- 8207426	29/06/83
FR-A- 2167355	28/09/73	NONE	